REMARKS

Claims 1-14, 18, 19, 46, 47, and 74-93 are pending in the present application.

The rejection of Claims 1-14, 18-19, 46-47, 74-82, 84-90, and 92-93 under 35 U.S.C. §102(b) over Merce-Vidal et al (English equivalent taken as CA 2466965) in view of Filla et al is respectfully traversed.

At the outset, Applicants wish to stress that the disclosure of Filla et al does not provide any basis to motivate the skilled person to change the $-(CH_2)_n-R^2$ moiety of Merce-Vidal et al to position 1 of the indole ring much less engender a reasonable expectation of success as alleged by the Examiner for the reasons that follow:

The Examiner's attention is first drawn to the fact that position 3 on the indole ring in Merce-Vidal et al is substituted by a $-(CH_2)_n-R^2$ moiety, wherein R^2 represents $-NR^4R^5$ or a specific non-aromatic nitrogen containing ring selected from a list of 11 different chemical formulae. On the contrary, position 1 on the indole in Filla et al does not contains the possibility of an amino-alkyl chain or a non-aromatic nitrogen containing ring. Further, position 5 on the compounds of Filla et al in comparison with Merce-Vidal et al is occupied by a different chemical group (sulfonic acid vs sulfonamide). Accordingly, both Merce-Vidal et al and Filla et al disclose indole compounds differing not only in the position of their substituents, but also in their nature.

Therefore, the skilled artisan, starting from Merce-Vidal et al would not have any basis and/or motivation to change the $-(CH_2)_n-R^2$ moiety to position 1, because this implies going beyond the teaching of both Merce-Vidal et al and Filla et al, as well as ignoring the recommendations of Filla et al for the specific substituents that are to be used at position 1 in

order to obtain compounds which are antagonists of the 5HT6 receptor. The definition of R in Filla et al is:

> *"R is hydrogen, Cl-C6 alkyl, substituted Cl-C6 alkyl, C3-C6 cycloalkyl, C1-C6 alkylsulfonyl, phenylsulfonyl, substituted phenylsulfonyl, naphthylsulfonyl, benzylsulfonyl, or substituted benzylsulfonyl;"*

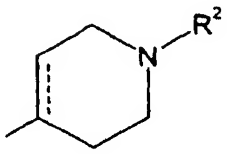
According to Filla et al (page 11, lines 31-37) preferred antagonists of 5-HT_6 receptor are compounds of formula I wherein **R** is hydrogen or C_1-C_6 alkyl, R and R^1 are taken together to form $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-CH_2-$, or R and R^4 are taken together to form $-CH_2-CH_2-CH_2-$.

From the foregoing, it is clear that the substituent R at position 1 on the indole in Filla et al does not include the groups disclosed in Merce-Vidal et al for position 3.

Thus, in the unlikely event that the skilled artisan would consider modifying the compounds of Merce-Vidal et al in order to introduce a substituent at position 1 on the nitrogen atom of the indole ring, which is a very specific position, he would always consider the substituents proposed by Filla et al for this position, and no others. There is no reason to ignore the substituents proposed by Filla et al, and take instead the substituent that is at position 3 in Merce-Vidal et al.

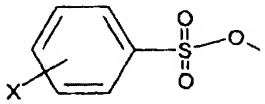
It is also important to note that the substituents of a chemical compound may not be interpreted in isolation. In the present case, the general formula of the indole derivatives disclosed in Filla et al have two additional substitutions clearly unrelated to the compounds of the present invention, namely:

- Position 3 of the indole derivatives of the present invention does not allow an heterocyclic moiety other than an heteroaryl radical, which implies aromaticity. On the contrary, in Filla et al the moiety



is mandatory in position 3 of the indole ring, as stated in the general formula (I) of said application.

- Position 5 of the indol-5-yl sulfonamide derivatives of the present invention is always substituted by a sulfonamide moiety, whereas said position is necessary substituted by a sulfonic acid moiety in Filla et al, as stated in the general formula (I) of the application, concretely by the following moiety



In view of the foregoing and in response to the Examiner's allegations in paragraph 23 of the Office Action mailed February 19, 2009, Applicants again submit that Merce-Vidal et al fail to provide any disclosure or suggestion of how their compounds may be or should be modified to arrive at the claimed compounds. Filla et al do not compensate for this defect. To this end, Applicants direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v.*

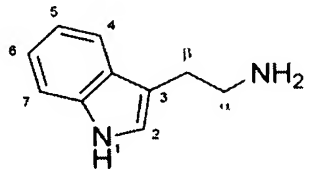
Teleflex Inc., 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight"to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

In view of the foregoing, Applicants submit that the present invention is not obvious in view of Merce-Vidal et al or Filla et al as these references fail to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, Merce-Vidal et al and Filla et al fail to support even a *prima facie* case of obviousness.

Moreover, in response to the Examiner's comments appearing in paragraphs 20-22 of the Office Action mailed February 23, 2009, Applicants provide the following response, which further illustrates why Merce-Vidal et al and Filla et al fail to meet the standard for obviousness set forth in *Takeda* and, even if they did, why the claimed invention still would not be obvious.

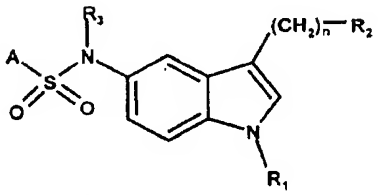
In response to the Examiner's allegations in paragraph 20 "First", Applicants again submit that, in contrast to the indole compounds disclosed in Merce-Vidal et al and Filla et al, the compounds of the present invention do not have a tryptamine-like structure.



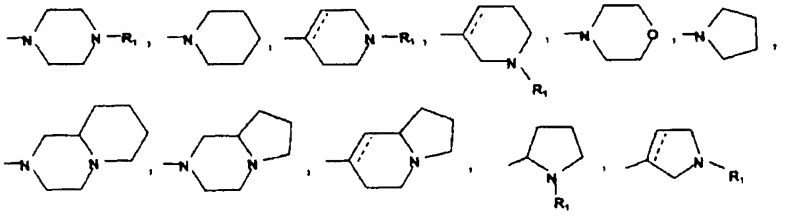
tryptamine

As may be observed, the general formulae described both in Merce-Vidal et al and Filla et al are 2-aminoalkyindoles:

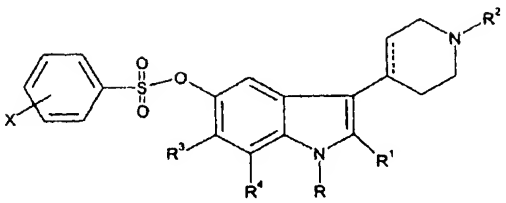
Merce-Vidal et al.



R_2 represents $-NR_4R_5$ or a group with formula:



Filla et al.



As stated for instance in Sophie-Isabelle Bascop et al., *Arkivoc* **2003** 46-61, 2(3)-aminoalkyl indoles (tryptamine, homotryptamine and isotryptamine related derivatives) have attracted considerable interest as potent and selective serotonin receptor ligands, such as 5-HT_6 receptor. Some documents reporting this structure-activity relationship are shown hereinunder:

- "2-Substituted Tryptamines: Agents with Selectivity for 5-HT6 Serotonin Receptors", Richard A. Glennon et al., *J. Med. Chem.*, **2000**, *43* (5), pp 1011–1018

- "N1-(Benzenesulfonyl)tryptamines as novel 5-HT6 antagonists", Yuching Tsai et al., *Bioorganic & medicinal chemistry letters* **2000**, vol. 10, no 20, pp. 2295-2299
- "5-halo-tryptamine derivatives used as ligands on the 5-HT6 and/or 5-HT7 serotonin receptors", US 7098233

Therefore, in the present application, the skilled artisan would not have found it reasonable and/or apparent to move the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring as discussed above because such movement *would involve the rupture of the tryptamine-like structure*, which was considered essential for the activity as shown in Merce-Vidal et al and Filla et al.

In response to the Examiner's allegations in paragraph 21 "Second", the shift of -$(CH_2)_n$-R^1 from position 3 on the indole ring (as in Merce-Vidal et al) to position 1 on the indole ring (as in the instant application) is not irrelevant. The Examiner's attention is drawn to MPEP 2144.09 which states:

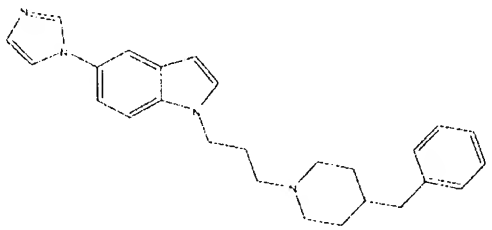
> "*Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by –CH_2- groups) are* ***generally*** *of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder 563 F.2d 457, 195 USPQ 426 (CCPA 1977).*" (emphasis added)

Thus, even it were the case that the claimed compounds are simply position isomers or homologs of the compounds disclosed by Merce-Vidal et al Applicants, which would bear the burden of proof, have provided bibliographic evidences in the response filed on November 28, 2008 to prove that the different biological properties between 1-substituted and 3-substituted indoles are known from the prior art. The documents provided (WO 9320065 vs Russell, M.G.; *J. Med. Chem.*; (**1999**); 42(24); 4981-5001; Liou, J.P.; *J. Med.*

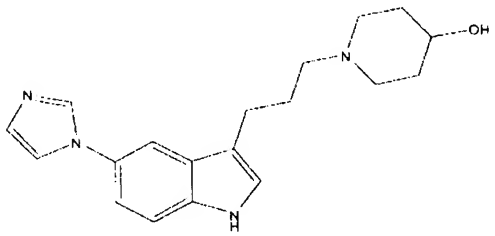
Chem.; (**2007**); 50(18); 4548-4552 vs Leonard, B.E.; *Neuropharmacology*; (**1972**); 11(3); 373-384) show how such positional isomers not only can have a different activity regarding the same receptor, but also their activity can be associated with different receptors, which implies totally different medical uses.

Specifically, Merce-Vidal et al provides no hint as to moving the amino moiety or the *N*-containing cycloaliphatic ring to the 1-position of the indole ring without losing affinity for the 5-HT_6 receptor.

In addition, the Examiner's assertions do not stand comparison with similar situations described in the state of the art. For example, compound (1) is claimed as inhibitor of thromboxane A2 synthesis in WO 9320065, while compound (2), having a similar substituent but in position 3, is described as highly selective h5-HT1D receptor agonist in Russell, M.G.; *J. Med. Chem.*; (**1999**); 42(24); 4981-5001.

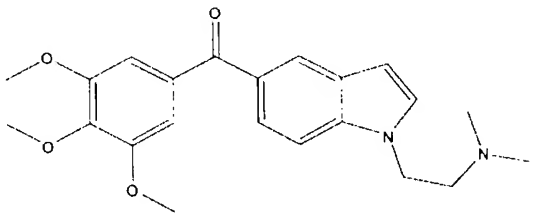


Compound (1)

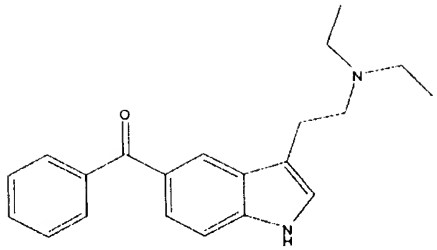


Compound (2)

A similar situation arises when comparing compound (5), which is described as potent antitubulin agent in Liou, J.P.; *J. Med. Chem.*; (**2007**); 50(18); 4548-4552, with compound (6) of Leonard, B.E.; *Neuropharmacology*; (**1972**); 11(3); 373-384, which is described as having effects on brain monoamines and their precursor amino acids.



Compound (5)

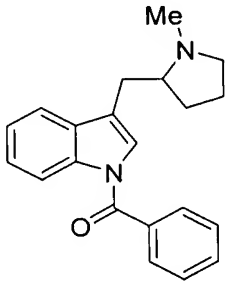


Compound (6)

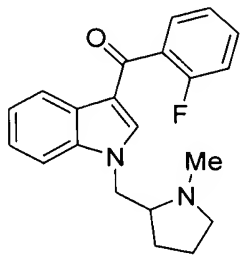
Thus, the skilled artisan when considering Merce-Vidal et al in light of the prior art, could expect changing the $-(CH_2)_n-R^2$ moiety to position 1 to have dramatic changes in the properties of the resulting compounds. Neither Merce-Vidal et al nor Filla et al provide any reasonable basis to conclude that making the substitutions and modifications to the compound disclosed by Merce-Vidal et al based on Filla et al would have similar activity.

Despite the foregoing, the Examiner alleges that this showing is not persuasive because none of the compounds referenced is drawn to modulators of 5-HT_6. Even though Applicants maintain that the foregoing is germane to the question at hand, they provide an example of two different compounds that can be associated with a "positional isomerism" for which US patents have been granted: one of them proposed as 5-HT_6 antagonist and the other proposed for treating intraocular pressure or glaucoma, which are not related to 5-HT_6 receptor. Such compounds are respectively:

- RN: 244122-12-1 US 6,100,291 granted on August 8, 2000;



- RN: 137642-51-4 US 5,607,933 granted on April 3, 1997.



As complementary note, it is remarkable that 244122-12-1, which has a tryptamine-like structure, acts as 5-HT_6 antagonist whereas when the pyrrolidinalkyl moiety is moved to position 1 (137642-51-4), the compound is indicated for disorders not related to said receptor such as the reduction of intraocular pressure.

Thus, the skilled artisan considering Merce-Vidal et al in light of the aforementioned art, could expect changing the $-(CH_2)_n-R^2$ moiety to position 1 to have dramatic changes in the properties of the resulting compounds.

In response to the Examiner's allegations in paragraph 22 "Third", the Examiner's attention is drawn to example 25 described in Filla et al, which represents a 1-(2-pyridyl)methyl indole. As stated previously, pyridyl groups are not comprised within the definitions for R^2 in Merce-Vidal et al. Therefore, it is doubtful that the skilled artisan would have reasonably predicted the $-(CH_2)_n-R^2$ moiety attached to position 3 on the indole ring in Merce-Vidal et al could be shifted to position 1 in the light of example 25 of Filla et al. Even if this were the case, the moiety 1-(2-pyridyl) is not within the definitions of R^1 in the presently claimed invention. .

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The provisional obviousness-type double patenting rejections over US 10/566,101 (now US 7,462,640) in view of Laconde et al and US 10/566,403 (now US 7,414,070) in view of Laconde et al, are obviated the Terminal Disclaimer **submitted herewith**.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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